

**DRAFT
TOXICOLOGICAL PROFILE FOR
ATRAZINE**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry**

September 2001

DISCLAIMER

The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.

UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

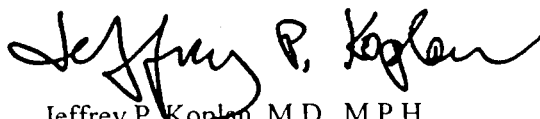
Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road, N.E.
Mail Stop E-29
Atlanta, Georgia 30333

Background Information

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on October 21, 1999 (64 FR 56792). For prior versions of the list of substances, see *Federal Register* notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); and November 17, 1997 (62 FR 61332). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

A handwritten signature in black ink, reading "Jeffrey P. Koplan". The signature is fluid and cursive, with the first name "Jeffrey" being more prominent and the last name "Koplan" following in a similar style.

Jeffrey P. Koplan, M.D., M.P.H.

Administrator

Agency for Toxic Substances and
Disease Registry

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	How Can (Chemical X) Affect Children?
Section 1.7	How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7	Children's Susceptibility
Section 6.6	Exposures of Children

Other Sections of Interest:

Section 3.8	Biomarkers of Exposure and Effect
Section 3.11	Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-888-42-ATSDR or (404) 498-0110

Fax: (404) 498-0057

E-mail: atsdric@cdc.gov

Internet: <http://www.atsdr.cdc.gov>

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards*; *Skin Lesions and Environmental Exposures*; *Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: <http://www.aeec.org/>.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

Alfred Dorsey
ATSDR, Division of Toxicology, Atlanta, GA

Susan S. Little, PhD
Syracuse Research Corporation, Atlanta, GA

David B. Knaebel, PhD
Syracuse Research Corporation, Syracuse, NY

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

PEER REVIEW

A peer review panel was assembled for atrazine. The panel consisted of the following members:

1. James E. Klaunig, Ph.D., Professor of Pharmacology and Toxicology, Director, Division of Toxicology, Indiana University School of Medicine, 135 Bennington Drive, Zionsville, Indiana 46077;
2. Kannan Krishnan, Ph.D., Associate Professor, Department of Occupational and Environmental Health, University of Montreal School of Medicine, 2375 Chemin de la Cote Ste-Catherine, Montreal, Quebec H3T 1A8; and
3. Frederick Oehme, D.V.M, Ph.D., Professor of Toxicology, Pathobiology, Medicine, and Physiology, Director, Comparative Toxicology Laboratories, Department of Diagnostic Medicine/Pathobiology, Kansas State University, 1800 Dennison Avenue, Mosier Hall, Manhattan, Kansas 66506-5606.

These experts collectively have knowledge of atrazine physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

CONTENTS

FOREWORD	v
QUICK REFERENCE FOR HEALTH CARE PROVIDERS	vii
CONTRIBUTORS	xi
PEER REVIEW	xiii
LIST OF FIGURES	xix
LIST OF TABLES	xxi
1. PUBLIC HEALTH STATEMENT	1
1.1 WHAT IS ATRAZINE?	1
1.2 WHAT HAPPENS TO ATRAZINE WHEN IT ENTERS THE ENVIRONMENT?	2
1.3 HOW MIGHT I BE EXPOSED TO ATRAZINE?	3
1.4 HOW CAN ATRAZINE ENTER AND LEAVE MY BODY?	4
1.5 HOW CAN ATRAZINE AFFECT MY HEALTH?	5
1.6 HOW CAN ATRAZINE AFFECT CHILDREN?	6
1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ATRAZINE?	7
1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ATRAZINE?	8
1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?	8
1.10 WHERE CAN I GET MORE INFORMATION?	9
2. RELEVANCE TO PUBLIC HEALTH	11
2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ATRAZINE IN THE UNITED STATES	11
2.2 SUMMARY OF HEALTH EFFECTS	12
2.3 MINIMAL RISK LEVELS	14
3. HEALTH EFFECTS	17
3.1 INTRODUCTION	17
3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE	17
3.2.1 Inhalation Exposure	18
3.2.1.1 Death	18
3.2.1.2 Systemic Effects	18
3.2.1.3 Immunological and Lymphoreticular Effects	18
3.2.1.4 Neurological Effects	18
3.2.1.5 Reproductive Effects	18
3.2.1.6 Developmental Effects	19
3.2.1.7 Cancer	19
3.2.2 Oral Exposure	19
3.2.2.1 Death	19
3.2.2.2 Systemic Effects	20
3.2.2.3 Immunological and Lymphoreticular Effects	50
3.2.2.4 Neurological Effects	51

3.2.2.5	Reproductive Effects	51
3.2.2.6	Developmental Effects	54
3.2.2.7	Cancer	57
3.2.3	Dermal Exposure	58
3.2.3.1	Death	58
3.2.3.2	Systemic Effects	58
3.2.3.3	Immunological and Lymphoreticular Effects	58
3.2.3.4	Neurological Effects	58
3.2.3.5	Reproductive Effects	59
3.2.3.6	Developmental Effects	59
3.2.3.7	Cancer	60
3.2.4	Other Routes of Exposure	61
3.3	GENOTOXICITY	62
3.4	TOXICOKINETICS	66
3.4.1	Absorption	66
3.4.1.1	Inhalation Exposure	66
3.4.1.2	Oral Exposure	67
3.4.1.3	Dermal Exposure	67
3.4.1.4	Other Routes of Exposure	68
3.4.2	Distribution	68
3.4.2.1	Inhalation Exposure	68
3.4.2.2	Oral Exposure	68
3.4.2.3	Dermal Exposure	69
3.4.2.4	Other Routes of Exposure	69
3.4.3	Metabolism	69
3.4.4	Elimination and Excretion	71
3.4.4.1	Inhalation Exposure	72
3.4.4.2	Oral Exposure	72
3.4.4.3	Dermal Exposure	72
3.4.4.4	Other Routes of Exposure	73
3.4.5	Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models	73
3.5	MECHANISMS OF ACTION	74
3.5.1	Pharmacokinetic Mechanisms	74
3.5.2	Mechanisms of Toxicity	76
3.5.3	Animal-to-Human Extrapolations	79
3.6	TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS	79
3.7	CHILDREN'S SUSCEPTIBILITY	81
3.8	BIOMARKERS OF EXPOSURE AND EFFECT	83
3.8.1	Biomarkers Used to Identify or Quantify Exposure to Atrazine	84
3.8.2	Biomarkers Used to Characterize Effects Caused by Atrazine	85
3.9	INTERACTIONS WITH OTHER CHEMICALS	86
3.10	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE	86
3.11	METHODS FOR REDUCING TOXIC EFFECTS	87
3.11.1	Reducing Peak Absorption Following Exposure	87
3.11.2	Reducing Body Burden	88
3.11.3	Interfering with the Mechanism of Action for Toxic Effects	88
3.12	ADEQUACY OF THE DATABASE	88
3.12.1	Existing Information on Health Effects of Atrazine	88
3.12.2	Identification of Data Needs	90
3.12.3	Ongoing Studies	100

4. CHEMICAL AND PHYSICAL INFORMATION	103
4.1 CHEMICAL IDENTITY	103
4.2 PHYSICAL AND CHEMICAL PROPERTIES	103
5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL	107
5.1 PRODUCTION	107
5.2 IMPORT/EXPORT	110
5.3 USE	110
5.4 DISPOSAL	111
6. POTENTIAL FOR HUMAN EXPOSURE	113
6.1 OVERVIEW	113
6.2 RELEASES TO THE ENVIRONMENT	116
6.2.1 Air	119
6.2.2 Water	120
6.2.3 Soil	120
6.3 ENVIRONMENTAL FATE	121
6.3.1 Transport and Partitioning	121
6.3.2 Transformation and Degradation	123
6.3.2.1 Air	124
6.3.2.2 Water	124
6.3.2.3 Sediment and Soil	125
6.3.2.4 Other Media	127
6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT	127
6.4.1 Air	127
6.4.2 Water	128
6.4.3 Sediment and Soil	131
6.4.4 Other Environmental Media	131
6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE	132
6.6 EXPOSURES OF CHILDREN	133
6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES	135
6.8 ADEQUACY OF THE DATABASE	136
6.8.1 Identification of Data Needs	136
6.8.2 Ongoing Studies	138
7. ANALYTICAL METHODS	143
7.1 BIOLOGICAL SAMPLES	143
7.2 ENVIRONMENTAL SAMPLES	145
7.3 ADEQUACY OF THE DATABASE	146
7.3.1 Identification of Data Needs	146
7.3.2 Ongoing Studies	149
8. REGULATIONS AND ADVISORIES	151
9. REFERENCES	161
10. GLOSSARY	193

APPENDICES

A.	ATSDR MINIMAL RISK LEVELS AND WORKSHEETS	A-1
B.	USER'S GUIDE	B-1
C.	ACRONYMS, ABBREVIATIONS, AND SYMBOLS	C-1
D.	INDEX	D-1

LIST OF FIGURES

3-1. Levels of Significant Exposure to Atrazine - Oral	39
3-2. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance	75
3-3. Existing Information on Health Effects of Atrazine	89
6-1. Frequency of NPL Sites with Atrazine Contamination	114

LIST OF TABLES

3-1. Levels of Significant Exposure to Atrazine - Oral	21
3-2. Levels of Significant Exposure to Atrazine - Dermal	44
3-3. Genotoxicity of Atrazine <i>In Vivo</i>	63
3-4. Genotoxicity of Atrazine <i>In Vitro</i>	64
3-5. Ongoing Studies on the Health Effects of Atrazine	101
4-1. Chemical Identity of Atrazine	104
4-2. Physical and Chemical Properties of Atrazine	105
5-1. Facilities that Produce, Process, or Use Atrazine	108
5-2. Registered Atrazine Manufacturing-use Products	109
6-1. Releases to the Environment from Facilities that Produce, Process, or Use Atrazine	117
6-2. Ongoing Studies on the Potential for Human Exposure to Atrazine	139
7-1. Analytical Methods for Determining Atrazine in Biological Samples	144
7-2. Analytical Methods for Determining Atrazine in Environmental Samples	147
7-3. Ongoing Studies on the Development of Analytical Approaches to the Study of Atrazine	150
8-1. Regulations and Guidelines Applicable to Atrazine	152